REMARKS

Reconsideration of this application, as amended, is respectfully requested.

The Examiner made the restriction requirement final and withdrew nonelected Claims 8-14 from consideration. In compliance with the statutory obligation, the present amendment cancels nonelected Claims 8-14 without prejudice to filing a divisional application in due course.

Pursuant to the Examiner's request, copies of the foreign references and the non-patent literature are supplied herewith to replace the misplaced copies originally furnished to the U.S. Patent and Trademark Office on December 12, 2000 and August 2, 2001. For the Examiner's convenience, duplicate copies of the original Form PTO-1449 or similar substitute form listing the patents or publications are also enclosed. Applicants respectfully ask that the Examiner consider the listed items, initial each form, return a copy thereof to Applicants with the next communication and enter the original form into the application file.

The Examiner rejects Claims 1 and 3 under 35 U.S.C. § 112, first paragraph, because the Examiner finds that the specification, while being enabling for the cytokine inducer compounds of formula I for the treatment of non-small cell type lung tumors with the co-administration with paclitaxel, does not provide enablement for using other cytokine inducer compounds or for the treatment of other types of tumors, for reasons set forth in the Office action on pages 5-10. To expedite matters but without comment on the merits of the rejection, Applicants have drawn Claim 1 to the preferred embodiment of the present invention, namely, the method of using the cytokine inducer compounds of formula I in combination with a chemotherapeutic agent to treat solid tumors. Applicants respectfully traverse the enablement rejection as it pertains to chemotherapeutic agent and treatment of solid tumors for the following reasons.

The Examiner has analyzed certain factors in determining whether Applicants' disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully disagree with both the analysis and the conclusions that the Examiner has drawn.

With respect to the state of the prior art, the Examiner cites Stein, M.D. (Fourth Edition (1994) of INTERNAL MEDICINE, Ed. J. H. Stein, M.D.) for the proposition that the treatment of solid tumors is highly unpredictable. Reading Chapters 71 and 72 entitled *Molecular and Cellular Biology of Cancer* and *Principles of Treatment of Cancer*, one of ordinary skill in the art would not come to the same conclusion. This Medical textbook summarizes the agents and

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

mechanisms of carcinogenesis along with current approaches to treatment that were known and available in 1994. On page 709, the textbook states: "[A] substantial decline has occurred in the mortality of patients with certain types of neoplastic disease. This is the direct result of systematic clinical trials that have tested various laboratory advances and/or clinical hypotheses." It further states: "The organ site and histologic classification obviously influence the treatment plan and prognosis (e.g., squamous cell versus small cell carcinoma of the lung). The specific features related to stage for most solid tumors are a function of their TNM characteristics: tumor size and local invasion (T), lymph nodal metastases (N), and metastases to other organs (M)." In effect, the textbook merely outlines the causes and common features of cancers. The textbook does not indicate or propose that the treatment of solid tumors by chemotherapeutic agents is highly unpredictable. In fact, the opposite is true. There is a wealth of knowledge that has enabled the significant decline of mortality from cancer.

Also, INTERNAL MEDICINE does not address all of the significant advances in oncology since 1994 until the date the present application was filed in the U.S. Patent and Trademark Office on September 12, 2000. Thus, it does not adequately reflect the state of the art on September 12, 2000. The Examiner's reliance on the citation is misplaced.

As applied to the claimed method, this textbook does not indicate or suggest that the ordinary practitioner would question the truth of Applicants' assertions that the compounds of formula I can be used with chemotherapeutic agents to treat solid tumors. There is no reason to believe otherwise.

With respect to the predictability or unpredictability of the art, the Examiner asserts that the physiological activity of a chemical or biological compound is considered to be an unpredictable art, citing examples of an angiotensin converting enzyme inhibitor, adrenocorticotropic hormones and RNA viruses. Rather than a blanket presumption of unknown predictability in the chemical or biological arts, this predictability factor refers to the ability of the ordinary chemist or biologist to extrapolate the disclosed results to the claimed invention. It does not require a disclosure of every operable species or exemplification of each and every embodiment. The predictability factor only determines if the ordinary practitioner would have reasonable doubt as to the accuracy of treating solid tumors with a combination of compounds of formula I and chemotherapeutic agents within the context of this invention as taught by the present

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

specification. The Examiner has not given any scientific principle or literature reference to prove any reasonable doubt in the oncology field.

With respect to the breadth of the claims, Claim 1 has been rewritten to draw the invention to the use of the compounds of formula I in combination with the chemotherapeutic agents. The ordinary practitioner would appreciate what to select for a suitable chemotherapeutic agent in order to treat the patient's particular solid tumor based on the teachings in the application (see, for example, the paragraph spanning pages 4 and 5) and the state of the art without undue experimentation.

With respect to the amount of guidance, it appears that the Examiner is only suggesting that the cytokine inducers, as previously claimed, have not been sufficiently exemplified in the application. Since the claims are now directed to the specific compounds of formula I, the amendment obviates this complaint.

With respect to the presence or absence of working examples as a factor for enablement, it is pointed out that there is no statutory requirement for working examples. Nevertheless, Applicants have provided sufficient exemplification including clinical trials of the use of the cytokine inducer compounds of formula I with paclitaxel and carboplatin as representative chemotherapeutic agents in the successful treatment of a non-small cell type lung tumor. It is more likely than not that another chemotherapeutic agent can be substituted for the paclitaxel and/or carboplatin with comparable results.

With respect to the quantity of experimentation necessary, it is within the ordinary skill of the art to understand how to replace the paclitaxel and/or carboplatin with another chemotherapeutic agent and expect similar benefits in combination with the compounds of formula I in treating solid tumors. It is simply a routine matter for the practitioner to follow the detailed instructions given from page 5, line 12 to page 7, line 6 and evaluate the combination through the standard *in vivo* pharmacological test procedure. Art-recognized cell lines may be readily substituted for the H-157 cell line to demonstrate anti-tumor activity against solid tumors such as breast, kidney, pancreas, *etc.* (see page 8, lines 14-16). Successful clinical trials, while not necessary for patentability, are also described in detail from pages 7 to 8. Based on the teachings in the specification, the practitioner would certainly be able to select and administer a suitable chemotherapeutic agent in the practice of the claimed method.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

There is no doubt that the practitioner would be able to practice the claimed invention without undue experimentation and, thus, the specification meets the statutory requirements. In view of the amendment and the foregoing comments, it is respectfully requested that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

The Examiner rejects Claims 1 and 3-7 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ayral-Kaloustian *et al.* (U.S. Patent No. 5,545,662) in view of The Merck Index. Applicants note but respectfully traverse the Examiner's rejection set forth on pages 2-4 and 12 of the Office action.

If the ordinary practitioner reads the '662 patent, it would be understood that the patent, as a whole, teaches that the compounds of formula I are useful as adjuvants to chemotherapy by restoring bone marrow function *after* chemotherapy and by ameliorating the neutropenia effect *caused by* the anticancer treatment. All of the examples show that the test formula I compound is given at least 24 hours *after* chemotherapy, which makes perfect sense in medical practice. The patient will not need to restore his or her bone marrow function or neutrophil count until after the chemotherapy is completed, not when it is started. Otherwise, it would be a waste of treatment. The '662 patent makes it clear by its examples that to achieve the effect of these compounds on neutrophil recovery and bone marrow function, the compound must be given at least 24 hours after chemotherapy.

In sharp contrast, the present invention is drawn to the unique method of treating solid tumors in which the combination is administered *during* chemotherapy. The compound of formula I must be given concurrently with the chemotherapy to effectively treat the solid tumors, not afterward. The formula I compound only works in the anti-tumor method of use during co-administration with the chemotherapeutic agent. Based on the '662 patent, there would be no motivation to give the formula I compounds during chemotherapy or to combine them with the chemotherapeutic agents of the cited Merck Index because the formula I compounds would not be effective or warranted in accelerating neutrophil recovery or restoring bone marrow function at that stage of treatment as taught by the patent.

Moreover, the patent does not teach that the compounds of formula I would even be useful to treat solid tumors. While patentees make the broad statement that the compounds can be used "in the treatment of" cancer, they only exemplify the beneficial post-chemotherapy use

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

to restore bone marrow function and neutrophil count. It clearly was not their intent at the time of the '662 patent to use formula I compounds in a method for treating solid tumors since the compounds of formula I are not anti-tumor agents. In point of fact, Applicants have demonstrated that the claim-recited compounds of formula I are totally devoid of anticancer activity; they did not inhibit tumor cell growth in nude mice or in tissue culture (see page 7, lines 1-6, of the application). Since the compound of formula I lacks efficacy in treating cancer and anti-tumor activity is not an inherent property, the ordinary practitioner would have absolutely no motivation to combine the compounds of formula I directly with chemotherapeutic agents to treat solid tumors. This pharmaceutical agent was not known to treat the very same ailment as the chemotherapeutic agent, namely cancer.

In view of the absence of anticancer activity, it is surprising that the claimed combination of the cytokine inducer and the chemotherapeutic agent would have synergistic activity against H-157 (see the excellent results in Table 1 on page 6 of the application). The clinical trial with cancer patients substantiates unforeseen potency of the novel chemotherapy treatment against late stage disease. The complete response rate with the combined therapy of paclitaxel and carboplatin is roughly only 5% but when the representative compound of formula I is added to the therapy, the cancer patients have an unexpected, significantly enhanced benefit in complete response (3 out of 6 patients), partial reduction in tumor mass (1 out of 6 patients) or stabilization of disease (1 out of 6 patients). The unexpected results show that the claimed method is not rendered obvious from the prior effect and use on bone marrow function and neutrophil recovery. The fact that the compounds of formula I are totally devoid of anticancer activity would negate any motivation for the skilled practitioner to combine the two pharmaceuticals for the claim-designated purpose. The practitioner would have no reasonable expectation that the formula I compounds could be successfully combined with chemotherapeutic agents to significantly improve the treatment of solid tumors. Since there is no reasonable expectation of success based on the established properties of the formula I compounds or the teachings in the '662 patent, the claimed method should be held patentable over the art (*In re Rinehart*, 531 F.2d 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991)).

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

The Examiner believes another motivation to combine the two biological agents to treat cancer would be found through the motivation to obviate multi-drug resistance of a chemotherapeutic agent. With all due respect, this is pure conjecture without support in the cited art. First of all, the '662 patent does not disclose or infer that the compounds of formula I have multi-drug reversing activity or that they could be used to increase the toxicity of a chemotherapeutic agent. Secondly, any motivation to obviate multi-drug resistance of a chemotherapeutic agent must come from what the cited references reasonably teach to one of ordinary skill in the art. Obviousness must not be found from hindsight vision based on the present application or "obvious to try" the claim-recited combination to treat solid tumors (*In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987)). Rather, the inability of the ordinary practitioner to predict the significantly improved results in treating cancer with the combination of the formula I compounds and the chemotherapeutic agents indicates that the claimed method is non-obvious from the teachings of the cited art.

The present invention is a solution to a different problem than the problem that the '662 patent solved. Patentees were interested in helping the patient recover bone marrow function and neutrophil count after chemotherapy. This application now provides a viable solution to the long-standing need in the art to find chemotherapeutic strategies that work successfully against highly fatal, solid tumors. Not only are they vastly different solutions to different problems, but also the compounds of formula I are not administered to the cancer patient on the same medication schedule. To restore bone marrow function or neutrophil count, the drug of formula I is administered *after* chemotherapy. In sharp distinction, the drug of formula I is given *during* chemotherapy to treat solid tumors. The oncologist would administer the compounds on a distinct schedule and for a different purpose based on the '662 patent than that of the instant method pursuant to the present teachings. This application, therefore, provides a new and non-obvious method of using the compounds of formula I that is performed at a different stage of cancer treatment and achieves a different end result than the methods taught in the '662 patent.

Applicants are not trying to patent an old combination. Rather, the present invention is drawn to a totally new and unique method of using the compounds of formula I in combination with the chemotherapeutic agents for the specific and claim-recited purpose of treating solid tumors. The '662 patent did not describe or propose this novel method of treatment.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

To summarize, the enhanced anti-tumor result of the claim-designated combination is totally unexpected since the compounds of formula I are devoid of anti-tumor activity. The new method of using the combination of the formula I compounds and the chemotherapeutic agents to treat solid tumors is not rendered obvious from the cited art. In view of the amendment and the foregoing comments, it is respectfully requested that the Examiner withdraw the rejection of Claims 1 and 3-7 under 35 U.S.C. § 103(a).

The Examiner maintains the rejection of Claims 1 and 3-7 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over Claims 1 and 2 of U.S. Patent No. 5,545,662 in view of The Merck Index for reasons given on page 14 of the Office action. Applicants respectfully traverse this rejection and contend that double patenting is not established by the facts.

The methods of restoring bone marrow function, increasing neutrophil counts or accelerating neutrophil recovery to combat the negative side effects of cancer chemotherapy do not imply a method of treating solid tumors. One method does not suggest the other to one of ordinary skill in the art. They are clearly not obvious variations of the same utility. They are independent and distinct methods that are performed at different treatment schedules and achieve totally different end results. To restore bone marrow function or increase neutrophil count, the drug is administered *after* chemotherapy. To treat solid tumors, the drug is given *during* chemotherapy. In sum, the patented claims and the present claims are distinguishable.

In view of the foregoing remarks, it is respectfully requested that the Examiner withdraw the obviousness-type double patenting rejection and allow the application.

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611

Accordingly, this application is now in condition for an allowance and such favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

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By: Anne M Rosenblum
Anne M. Rosenblum
Attorney for Applicants
Registration No. 30,419

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Anne M Rosenblum
Anne M. Rosenblum

ANNE M. ROSENBLUM ATTORNEY AT LAW
163 DELAWARE AVENUE - SUITE 212 • DELMAR, NEW YORK 12054 • TELEPHONE: (518) 475-0611